

REMARKS/ARGUMENTS

Claim Numbering

The examiner has pointed out that in the application as filed the claims were numbered 1-22 and 24-39. Applicants apologize for this typographical error, and hereby amend original claims 24-39 to their correct numbers 23-38. Hereinafter all references to claims will be to the correct numbers.

35 U.S.C. §112 Markush Language

Claims 9 and 34 have been rejected under 35 U.S.C. §112 the phrase “selected from” is allegedly improper Markush language. Applicants hereby amend claims 9 and 34 to replace the phrase “selected from” with the phrase “selected from the group consisting of.” Reconsideration and withdrawal of this rejection in view of this amendment is respectfully requested.

35 U.S.C. §112 Square Symbols

Claim 9 has been rejected because it contains square symbols, and repeated phrases. Applicants apologize for the typographical error of the square symbols. These square symbols were intended to be the symbols “ α and β ” and this portion of the claim was intended to read “... α -adrenergic agonists; β -adrenergic agonists; α -adrenergic blockers; β -adrenergic blockers (beta blockers)...” Applicants hereby amend the claim to include the “ α and β ” symbols. This amendment is supported on page 6 lines 7-8 of the specification. Reconsideration and withdrawal of this rejection in view of this amendment is respectfully requested.

35 U.S.C. §112 Optimal pH

Claims 21-22 have been rejected under 35 U.S.C. §112 because the term “optimal pH” is allegedly unclear. Beginning with the last paragraph on page 10, the specification provides a discussion of the use buffers of various pH's to “optimize the drug release profile, and optimize the degree of discrimination between important samples.” The optimization of pH is discussed on pages 11-13 of the specification. Example 3 of the present application provides an example

of pH optimization. Applicants respectfully submit that with this extensive disclosure, the person skilled in the art would the phrase “optimal pH.” Reconsideration and withdrawal of this rejection is respectfully requested.

Nonstatutory Obviousness-type Double Patenting Co-pending Application 10/658164

Claims 1-3, 5-25, 27 and 32-35 are provisionally rejected as being unpatentable over claims 1-2, 5-11, 13-17, 19, 21-24, 27 29-30 and 35 of co-pending Application No. 10/658,164. In support of this rejection, the examiner alleges that it would be obvious to one of ordinary skill in the art that an emulsion “inherently forms” as a result of contact and agitation of the aqueous dissolution medium and the non-aqueous liquid composition. To support a rejection based on inherency, it must be shown that an emulsion will always result when oil and water mixtures are agitated. The examiner has not provided any reference to support the allegation that the formation of emulsion is inherent when oil and water mixtures are agitated. In contrast, applicants have performed experiments which show that emulsions do not readily form when oil and water are simply stirred. As set forth on page 14 of the present specification:

Although they might be able to form an emulsion under special circumstances typically the non-aqueous liquid composition and the aqueous dissolution medium will not form an emulsion by simple stirring such as in a paddle assembly. In these apparatuses the non-aqueous liquid composition generally floats on the surface of the aqueous dissolution medium. Therefore, the area of contact between these two components is smaller than in the method of the invention and the dissolution rate of the analyte may be lower.

Figure 3 of co-pending Application No. 10/658,164 shows a paddle assembly suitable for use in the invention disclosed in the No. 10/658,164 application. As set forth above, Applicants have found that emulsion formation in such an apparatus is unlikely. Emulsion formation requires that the dispersed phase be broken up into the small droplets, which are dispersed in the continuous phase. Applicants respectfully note that as set forth beginning on page 12 line 25 of the No. 10/658,164 application it is desirable for the non-aqueous medium to spread on the

surface of the dissolution medium. It is optimal if the non-aqueous forms an even layer on the surface of the dissolution medium (page 13 line 3). Having the non-aqueous medium to spread in an even layer across the surface of the dissolution medium results in two distinct continuous phases. This is not the same as breaking up the non-aqueous phase into the small droplets which required for an emulsion. The examiner has noted that the No. 10/658,164 application fails to recite emulsion formation. Applicants respectfully suggest that the No. 10/658,164 application fails to recite emulsion formation because emulsion formation is not consistent with the method taught in the No. 10/658,164 application. In other words, the No. 10/658,164 application teaches a method which does not involve emulsion formation and thus teaches away from Applicants' invention. Reconsideration and withdrawal of this obviousness type double patenting rejection is respectfully requested.

35 U.S.C. §102(b) Dunn et al. (US 5,721,359)

Claims 1-2, 5-18, 22-23, 25 and 32-38 are rejected under 35 U.S.C. §102 as being allegedly anticipated by Dunn et al. In making this rejection the examiner states that in the dissolution test described in Dunn et al. the non-aqueous liquid composition and the aqueous are agitated with a paddle. The examiner further states that an emulsion is inherently formed. As set forth above emulsion formation is not inherent in paddle device. Furthermore, the dissolution test described in Example 7 of Dunn et al. does not allow contact between the aqueous dissolution medium, and the non-aqueous medium. The test is described in Dunn et al. as follows:

100 mg samples of crystalline ceftiofur free acid, amorphous ceftiofur free acid (prepared as described in Example 1) and crystalline ceftiofur hydrochloride, which were all prepared as oil formulations as described in Example 4 above, were loaded into teflon dissolution cells and sealed with a constant surface area dialysis membrane. The loaded cells were placed in a standard dissolution apparatus containing 500 ml of pH 7 aqueous dissolution media which was stirred by a 50 RPM rotating paddle.

Applicants respectfully note that the non-aqueous compositions are placed in a dissolution cell and sealed with a constant surface dialysis membrane. Accordingly, the non-aqueous composition is separated from the aqueous dissolution medium. Clearly an emulsion cannot form if the two phases are not in contact with each other. Since there is no possibility of emulsion formation in Dunn et al., the reference does not disclose Applicants' invention. Reconsideration and withdrawal of this rejection is respectfully requested.

35 U.S.C. §103(a) Dunn et al. (US 5,721,359) In View of Conti et al.

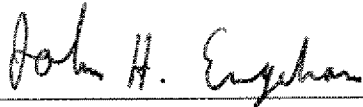
Claims 3-4, 19-21, 24 and 26-31 are rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Dunn et al. (US 5,721,359) in view of Conti et al. Applicants' invention relates to dissolution rate testing method in which intimate contact between the non-aqueous medium and the aqueous dissolution medium is promoted by forming an emulsion. Conti et al. relate to measurements of the rate of drug dissolution from drug containing microparticles in an aqueous medium. In other words Conti et al. relate to the dissolution of a drug from a solid phase into an aqueous phase. Conti et al. do not relate to a drug contained in a liquid non-aqueous medium which is in intimate contact with an aqueous medium. No emulsion is possible in Conti et al., and accordingly, the reference does not suggest Applicants' invention.

Dunn et al. do relate to a system of a non-aqueous medium containing a drug and an aqueous medium. However, these two phases are not in contact with each other, but are separated by a dialysis membrane during dissolution rate testing. No emulsion formation is possible under the conditions disclosed in Dunn et al. Applicants respectfully submit that by requiring the separation of the aqueous and the non-aqueous phases, Dunn et al. teach away from Applicants' invention.

Neither Conti et al. nor Dunn et al., either separately or combined, provide any teaching or suggestion of the use of an emulsion in dissolution rate testing. Thus, the combination of Conti et al. and Dunn et al. provide no suggestion Applicants' invention. Reconsideration and withdrawal of this rejection is respectfully requested. Reconsideration and withdrawal of all rejections and allowance of this application is respectfully requested.

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